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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,499	12/11/2001	Kevin P. Baker	39780-2830.42 US	6886

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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	**PAPER NUMBER**
1649	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/015,499	BAKER ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-35 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-35 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment filed on 7/25/07 has been entered.

2. Applicant's arguments filed 7/25/07 have been fully considered but they are not deemed to be persuasive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 28-35 & 38-40 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility, for the reasons made of record in Paper No: 20040913, 20050428 & 20070411, and as follows.

Applicants re-iterate arguments on pages 2-10 of the response that have previously been addressed, and therefore, remain not persuasive because the specification still does not identify a single "reasonable use" for the claimed *polypeptides* of the instant invention, because no "in general [consensus exists for] gene amplification increases mRNA expression" reasonably exists in the art, nor "in general, [is] there a [reasonable] correlation between mRNA levels and polypeptide levels", for the reasons previously made of record. In other words, even though "the present specification... discloses... evidence that ***the gene*** encoding the PRO1788 polypeptide is .:. amplified in colon tumors [emphasis added]", the claimed functional use of

"wherein the nucleic acid... is amplified..." for detecting colon tumors is not equivalent to identifying a use for PRO1788 mRNA, nor for extrapolating a use for the *claimed PRO1788 polypeptides* that are transcribed from PRO1788 mRNA, which further possess no known and distinguishable assayable activity. Likewise, as previously made of record, "increase in gene copy number" (i.e., DNA data) is not equivalent to increased mRNA levels, which are not equivalent to increased polypeptide levels (i.e., as claimed). Moreover, not a single submitted declaration has looked at PRO1788 mRNA and especially at PRO1788 polypeptide levels, which would be useful in establishing a *specific* utility for the instant invention, if correlated with increased DNA levels.

The issues then remain as follows:

1) both the instant specification and all of the currently submitted declarations fail to provide any information/data regarding increased polypeptide levels of PRO1788 in tumor samples relevant to normal samples. In contrast, Example 143 in the instant specification describes gene amplification assay data, which is well known in the art to measure DNA levels, and not mRNA levels, nor polypeptide levels. Because the instant claims are directed to PRO1788 *polypeptides*, it is, therefore, imperative to find evidence in the relevant scientific art as to whether or not a small increase in PRO1788 DNA levels (i.e., in which only one sample out of 17 colon tumors possessed a Ct level above 2.0, as it relates to colon DNA levels) would be considered by the skilled artisan to be predictive of an increase in subsequent PRO1788 mRNA levels and then be predictive of a subsequent yet distinct increase in polypeptide levels.

2) Polaski I's statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the

tumor cell relative to the normal cell", or Polaski II's statement that "there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA", are contradicted by the teachings of Pennica et al., who alternatively teach that although "*WISP-2* DNA was amplified in *colon tumors*, ... its *mRNA expression* was [conversely] significantly ***reduced** in the majority of tumors*... [emphasis added]". Likewise, Konopka (1986) state that "[p]rotein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Accordingly, the Scott Declaration statement that "direct measurement of protein expression levels remains non-trival" is the issue directly related to this rejection. Therefore, no dogma exists that DNA amplification results in mRNA overexpression, which then results in increased polypeptide levels (i.e., the claimed invention), and for the reasons previously made of record.

3) None of the cited references are further directed to analysis of multiple genes (with the exception of Futcher et al.), unlike the references of Chen et al. (analyzing 165 protein blots), Hu et al. (analyzing 2286 genes) and Haynes et al. (analyzing 80 genes/proteins) made of record by the Examiner, which alternatively caution researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (i.e., mRNA levels). Moreover, in contrast to Applicants' comments concerning Futcher, Futcher et al. still acknowledged that "Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance" (pg. 7397,col. 1, 1st pp).

Therefore, in contrast to Applicants' interpretation of the data of Chen et al., Hu et al., Haynes et al., Koponka et al. and Pennica et al., the issue remains that the specification fails to provide any evidence on whether or not the PRO1788 polypeptide levels are also increased in

these tumor samples. Given the evidence provided by Haynes et al., Hu et al. and Chen et al., who further look at multiple genes, it is clear that one skilled in the art would not assume that gene amplification, or increased mRNA expression, "more likely than not" would result in significantly increased polypeptide levels. Chen et al further drives home this point on page 304 (right column) by their description of the state of the art in that "[t]he use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-translational mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of protein present in a given cell or tissue". Likewise, Lewin acknowledges that "control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein...". Thus, "*more likely than not*" no generalized correlation exists between DNA amplification resulting in mRNA overexpression, which then results in a subsequent increase in polypeptide levels, and for the reasons previously made of record.

4) Additionally, neither Orntoft, Hyman, Pollack, Bea nor Godbout show a "general" mRNA/protein correlation, for the reasons previously made of record. In fact, none of the cited references look at DNA/protein correlations. In particular, neither Hyman nor Pollack looked at polypeptide levels, in which Hyman further stated that less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Thus, Applicants' arguments remain not on point with the fact situation in the instant case, and therefore, remain not persuasive, because gene expression data alone (i.e., DNA; as it relates to the instant specification) is not equivalent to mRNA data, which is not equivalent to polypeptide data, in contrast to Applicants' assertions. It is again pointed out that Applicants have also previously acknowledged that "the correlation

between mRNA and protein level is not exact" (see page 17 of the previous response), and therefore, cannot be "more likely than not true", by definition.

Therefore, the issue remains that the instant specification provides no information/ data regarding increased *protein* levels of PRO1788 in tumor samples relevant to normal samples, and therefore, provides no reasonable *specific* use for the claimed PRO1788 *polypeptides* related to SEQ ID NO: 397. In other words, gene amplification data alone (i.e., increased DNA levels in 8 of 17 colon tumors; as it relates to the instant specification) is not equivalent to polypeptide data. In the absence of any of the above information, all that the specification does is invite the artisan to determine the significance of this "amplification", as it relates to polypeptide function and expression. Thus, the specification merely presents an invitation for others to experiment and discover a use for the claimed polypeptides at the time of filing the instant invention.

As previously made of record, a utility of being a diagnostic target for colon tumors is a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use, because amplification of DNA in colon tumors is not the same as showing PRO1788 protein causes colon cancer, and because it is not known whether PRO1788 mRNA or protein is expressed in corresponding normal colon tissues, or what the relative levels of expression are. All that the specification does is invite the artisan to determine the significance of this "gene amplification". This is not a *substantial utility*, by definition.

In conclusion, for the reasons discussed above and previously made of record, because the proposed use of the PRO1788 polypeptides of the instant invention are simply starting points for further research and investigation into potential practical uses of the polypeptides related to

SEQ ID NO: 397, the instant claims have no specific nor substantial utility, consistent with that held by the court in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966):

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

5. Claims 28-35 & 38-40 stand also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for the reasons made of record in Paper NOs: 20040913, 20050428 & 20070411.

6. Claims 28-32 & 39-40 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons made of record in Paper NOs: 20040913, 20050428 & 20070411, and as follows.

In summary, a recitation related to "wherein the nucleic acid... is amplified..." does not reasonably constitute a "functional limitation" for the claimed polypeptides. The specification has further not described or shown possession of polypeptides 80-99% homologous to SEQ ID NO: 397, which retain the function of SEQ ID NO: 397, if later discovered. Nor have Applicants

described a representative number of species that have 80-99% homology to SEQ ID NO: 397, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 397; consistent with that held by the court in *Vas-Cath Inc. v. Mahurkar* previously made of record.

As previously made of record, page 301 of the specification specifically states that "[t]he PRO polypeptides described herein *may be isolated from a variety of sources*, such as from human tissue types *or from another source*... [emphasis added]" . In contrast, the sole single *human* polypeptide species described is PRO1788 of SEQ ID NO: 397. No written description is provided in the specification for any other species of PRO1788 molecules, in which disclosure of a single *"human"* polypeptide sequence does not reasonably constitute "the claimed genus of polypeptides". Therefore, Applicants are clearly not in compliance with the written description requirement under 35 U.S.C. 112, first paragraph, for the reasons made of record, which are consistent with that held by the courts in *Fiers v. Revel*, *Fiddes v. Baird*, and *Univ. California v. Eli Lilly and Co.*, previously made of record. See again MPEP 2163.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday, from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Stucker, can be reached on (571) 272-0911. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
February 19, 2008

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER